**REMARKS**

Claims 12-14, 18 and 22-29 are pending in this application. Claims 14, 28 and 29 have been canceled. Claims 12, 13, 18, 22, 23 and 24 have been amended. Claim 30 has been added to re-introduce to subject matter of claim 18 prior to this amendment. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks and amendments.

**I. Rejection of Claims 12-14 and 18 under 35 U.S.C. §112, first paragraph**

The Examiner has rejected claims 12-14 and 18 under 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The Examiner has acknowledged that the specification is enabling for a method of sensitizing tumor cells to chemotherapeutic prodrug APC or CPT-11 *in vitro,* comprising transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase

operably linked to a promoter which directs specific expression of said carboxylesterase in said tumor cells, wherein expression of the carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of the chemotherapeutic drug. It is further acknowledged that a method of inhibiting tumor cell growth *in vitro* comprising sensitizing tumor cells by transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter which directs specific expression of said carboxylesterase in said tumor cells and contacting said tumor cells with chemotherapeutic prodrug APC or CPT-11 so that the tumor growth is inhibited, is enabled. It is yet further acknowledged that the previously stated methods may be applied *in vivo* wherein the polynucleotide encoding the rabbit carboxylesterase is carried by an adenoviral vector which is administered intratumorally or intravenously and the chemotherapeutic drug is administered intravenously. The Examiner further acknowledges that there is no undue experimentation in identifying CE that is able to cleave CPT-11 by the computer model. The Examiner yet further acknowledges that the computer model taught by Applicants, successfully

confirms another type of carboxylesterase can cleave CPT-11 type of prodrug.

It is suggested, however, that such methods do not reasonably provide enablement for such method of *in vivo* application where the polynucleotide encodes any carboxylesterase and the said enzyme and chemotherapeutic drug are delivered by any route. Applicants respectfully disagree.

However, in an earnest attempt to facilitate prosecution of this application, Applicants have amended claims 12, 13 and 18 accordance with the suggestions and acknowledgments of enabled subject matter as recited by the Examiner. It is respectfully pointed out that claims 12 and 13 were not further limited to rabbit CE, as the prodrug was limited to CPT-11 or APC, but that rabbit CE is specifically claimed in claim 23. Applicants hereby reserve the right to pursue any or all canceled subject matter in a divisional application.

Claim 12 has been amended to recite a method for sensitizing tumor cells to a chemotherapeutic prodrug APC or CPT-11 *in vitro* comprising transfecting selected tumor cells with a composition comprising an isolated polynucleotide encoding a carboxylesterase wherein said carboxylesterase is operably linked to a promoter that directs expression of said carboxylesterase in said tumor

cells, and wherein expression of the carboxylesterase renders the tumor cells more sensitive to the cytotoxic effect of said chemotherapeutic prodrug APC or CPT-11. The scope of claim 12 as amended has been acknowledged to be enabled by the Examiner.

Withdrawal of the rejection and allowance of claim 12 is hereby respectfully requested.

Claim 13 has been amended to recite a method of inhibiting tumor cell growth *in vitro* comprising: (A) sensitizing tumor cells in accordance with the method of claim 12; and (B) contacting said sensitized tumor cells with said chemotherapeutic prodrug CPT-11 or APC so that tumor cell growth is inhibited. In view of this amendment, claim 14 has been canceled herewith, as the limitation is now incorporated into claim 13. The scope of claim 13 as amended has been acknowledged to be enabled by the Examiner.

Withdrawal of the rejection and allowance of claim 13 is hereby respectfully requested.

Claim 18 has been amended to recite a method of inhibiting tumor growth in a patient comprising administering to a patient a composition comprising an isolated polynucleotide encoding a rabbit carboxylesterase capable of cleaving a chemotherapeutic prodrug and inactive metabolites thereof to active drug, wherein

said rabbit carboxylesterase is operably linked to a promoter that directs expression of said rabbit carboxylesterase in a tumor, wherein the dosage of said composition is one determined to produce the longest delay of recurrent disease and wherein the composition is carried by an adenoviral vector which is administered intratumorally or intravenously, and wherein the chemotherapeutic drug is administered intravenously. The scope of claim 18 as amended has been acknowledged to be enabled by the Examiner.

Withdrawal of the rejection and allowance of claim 18 is hereby respectfully requested.

For ease of prosecution, Applicants have amended claim 18, to present the claim as acknowledged to be enabled by the Examiner, as set forth above. Applicants are herewith re-presenting the subject matter of claim 18 (prior to amendment herewith) as new claim 30, and have limited the prodrug to APC or CPT-11, reconsideration is requested in light of the following comments.

Claim 30 recites a method of inhibiting tumor growth in a patient comprising administering to a patient a composition comprising an isolated polynucleotide encoding a carboxylesterase capable of cleaving a chemotherapeutic prodrug APC or CPT-11 and

inactive metabolites thereof to active drug, wherein said carboxylesterase is operably linked to a promoter that directs expression of said carboxylesterase in a tumor, wherein the dosage of said composition is one determined to produce the longest delay of recurrent disease.

The Examiner acknowledges in the present office action (at page 2) that the specification is enabling for a method of sensitizing tumor cells to a chemotherapeutic prodrug APC or CPT-11, *in vitro.* The Examiner further acknowledges in the present office action (at page 5) that there is no undue experimentation in identifying CE that is able to cleave CPT-11 by the computer model. The Examiner yet further acknowledges that the computer model taught by Applicants, successfully confirms another type of carboxylesterase can cleave CPT-11 type of prodrug.

The Examiner has further acknowledged that Declaration 2 (July 9, 2003) demonstrates successful expression of human intestinal carboxylesterase (hiCE) by two herpes simplex viral vectors in a human glioma cell line. However, the Declaration 2 (July 9, 2003) is suggested to fail to provide further evidence that such *in vitro* expression would translate into expression at sustained and high enough levels *in vivo* to sensitize tumor cells to chemotherapeutic drug. The Examiner further suggests that

successful delivery by any of multiple routes as set forth in the specification and Declaration 2, *in vivo* is not enabled. Applicants respectfully disagree.

First, Section 2107.02 of the MPEP states "if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process". Section 2107.02 of the MPEP further states "The applicant does not have to prove that a correlation exists between a particular activity and an assorted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted".

Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use *Nelson v. Bowler,* 626 F.2d 853, 857, 206 USPA 881, 884 (CCPA 1980).

In addition, the courts have held that it is only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility, does the burden shift to the applicant to provide rebuttal evidence sufficient to

convince such a person of the invention's asserted utility. See *In re Bundy,* 209 USPQ 48, 51 (CCPA 1981).

As evidenced by the Declaration 2 (July 9, 2003), a reasonable correlation between the CE expression or activity and the asserted use of sensitizing tumor cells *in vivo* exists using vectors other than only adenoviral vectors. The compositions are demonstrated and acknowledged to be successfully carried by adenoviral vectors and herpes viral vectors, see Examiner's comments in the Office action dated September 24, 2003 and see, Declaration 1 and Declaration 2. Based upon the data generated and the two Declarations by experts in this field, it is believed that the invention can be practiced using multiple gene delivery systems, i.e., herpes simplex viral vectors, retroviruses, vaccinia viruses, adeno-associated viruses, chemical mediated gene transfer, receptor mediated DNA uptake, neural stem cell and physical transfer by gene guns or electroporation, as set forth in Declaration 2 (July 9, 2003), at paragraph 4.

Thus, Applicants respectfully assert that the PTO has not satisfied its initial burden with regard to limiting the use of delivery systems taught by Applicants, namely, herpes simplex viral vectors, retroviruses, vaccinia viruses, adeno-associated viruses, chemical mediated gene transfer, receptor mediated DNA

uptake, neural stem cell and physical transfer by gene guns or electroporation.

Applicants should not have to substantiate a presumptively correct disclosure, and limit the *in vivo* delivery to only adenoviral vectors, to avoid a rejection under the first paragraph of section 112. As shown in Declaration 2 at paragraphs 3 through 4, the data relating to the increased expression of CE activity in tumors injected with the subject Herpes vectors alone should be sufficient to satisfy Applicants' burden, as a matter of law.

Further, the data relied upon in the Declaration 2(July 9, 2003), and Declaration 1 (November 18, 2002) demonstrate the effectiveness of rabbit CE, human intestinal CE and bacterial CE expression for cleaving a prodrug. Further yet, the Examiner has acknowledged (page 5, Office action mailed September 24, 2003) that other CEs which cleave CPT-11 may be routinely identified without undue experimentation. Applicants have demonstrated that various carboxylesterases can be used to activate a prodrug such as CPT-11. *In vivo* experiments using the human intestinal carboxylesterase are found on page 40, lines 20 through page 41, line 2. Other experiments showing the use of human intestinal carboxylesterase are found throughout the specification.

Declaration 2 at paragraphs 6-7 and Figure 2 further show additional information which corroborate that CEs other than rabbit, could be used in the invention, i.e., a bacterial carboxylesterase is capable of activating CPT-11. Further, the bacterial carboxylesterase was identified using the assays outlined in the specification.

In light of these remarks and the Examiner's acknowledgments of enabled subject matter, Applicants believe that they have satisfied their burden under 35 USC 112, and have demonstrated sufficient correlation between identifiable CEs and their therapeutic use in cleaving CPT-11 or APC. Further, Applicants believe that they have demonstrated sufficient correlation between the taught delivery systems and their ability to be useful in increasing the expression of CE activity in tumors.

Withdrawal of the rejection and allowance of claim 30 is hereby respectfully requested in view of these remarks.

**II. Written Description**

The Examiner suggests that claims 12-14 and 18 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors

had possession of the claimed invention. It is suggested that the previous arguments filed July 9, 2003 did not address the written description rejection. It is suggested that the specification fails to disclose the successful use carboxylesterase other than rabbit. It is further suggested that a structural-functional relationship is not described in the specification for either the term "carboxylesterase capable of cleaving a chemotherapeutic prodrug" or a chemotherapeutic prodrug capable of being cleaved by a carboxylesterase.

Applicants respectfully disagree.

As is clearly recited in the response filed July 9, 2003, Applicants have clearly taught the use of more than one carboxylesterase in the application. *In vivo* experiments using the human intestinal carboxylesterase are found on page 40, lines 20 through page 41, line 2. Other experiments showing the use of human intestinal carboxylesterase are found throughout the specification. Declaration 2 at paragraphs 6-7 and Figure 2 further show additional information which corroborate that other CEs could be used in the invention, i.e., a bacterial carboxylesterase is capable of activating CPT-11. Further, the bacterial carboxylesterase was identified using the assays outlined in the specification.

Further, it is acknowledged by the Examiner that there is no undue experimentation required to identify CEs capable of cleaving a prodrug such as CPT-11 type, or APC, using the computer model described in Applicant's specification at page 24, lines 15-24 for predicting carboxylesterases capable of cleaving CPT-11 via a computer modeling method; on page 30, line 8 through page 31, line 3, and on page 35 line 22 through page 36, line 18 for an assay system for testing the carboxylesterase cleaving ability.

As further corroboration, Declaration 2 at paragraph 6, shows that yet another carboxylesterase, the pnbA gene from *Bacillus subtilis* is capable of cleaving a prodrug and that this carboxylesterase was identified using the methods described in the specification. An assay provides means for identifying other additional carboxylesterases which is clearly within the skill of one in the art, as taught by the specification at page 30, line 8 through page 31, line 3 and page 35, line 22 through page 36, line 18. Therefore, Applicants have provided methods to identify which carboxylesterases will work without undue experimentation and data proving those methods will work with multiple carboxylesterases. Applicants have further shown that drugs

other than CPT-11 and APC are capable of being cleaved by a carboxylesterase without undue experimentation.

However, in an earnest attempt to facilitate the prosecution of this application, and as acknowledged to be enabled by the Examiner, Applicants have amended claims 12, 13 and 18 to recite the use of chemotherapeutic prodrug APC and CPT-11, thus identifying a structural and functional relationship between the prodrug and the carboxylesterase. With regard to claims 12 and 13, the Examiner has acknowledged in the present office action (at page 2) that the specification is enabling for a method of sensitizing tumor cells to a chemotherapeutic prodrug APC or CPT-11, *in vitro*. The Examiner further acknowledged in the present office action (at page 5) that there is no undue experimentation in identifying CE that is able to cleave CPT-11 by the computer model. Further, claim 18 has been limited to adenoviral vector delivery systems and use rabbit carboxylesterase, for reasons set forth fully above. Applicants believe that the written description requirement for claims 12-14 and 18 is satisfied in view of these amendments.

Applicants respectfully request reconsideration and withdrawal of this rejection.

**III. Rejection of Claims 12-14, 18 and 22-29 under 35 U.S.C. §112, second paragraph**

The Examiner has rejected claims 22 -24 under 35 U.S.C. §112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner suggests that regarding claim 22, the recitation of the carboxylesterase is selected from the group consisting of rabbit polynucleotide and human intestinal polynucleotide renders the claim indefinite because it is unclear how the carboxylesterase can be a rabbit or human intestinal polynucleotide. Clarification is requested by the Examiner.

In accordance with the Examiner's suggestion, and in an earnest attempt to facilitate prosecution, claim 22 has been amended to clarify that carboxylesterase is selected from the group consisting of rabbit carboxylesterase and human intestinal carboxylesterase. Support for this amendment is found throughout the specification and at page 40, lines 12-24. Withdrawal of this rejection is respectfully requested.

The Examiner suggests that with regard to claims 23 and 24, the recitation of "the carboxylesterase comprises a rabbit

polynucleotide" or "the carboxylesterase comprises a human intestinal polynucleotide" renders the claim indefinite. Clarification is requested by the Examiner.

In accordance with the Examiner's suggestion, and in an earnest attempt to facilitate prosecution, claims 23 and 24 have been amended to clarify that "the carboxylesterase comprises a rabbit carboxylesterase" or "the carboxylesterase comprises a human intestinal carboxylesterase" Support for this amendment is found throughout the specification and at page 40, lines 12-24. Withdrawal of this rejection is respectfully requested.

**IV. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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